UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

ROCHE DIAGNOSTICS GMBH and ROCHE MOLECULAR SYSTEMS, INC., Plaintiffs and Counterclaim Defendants, v. ENZO BIOCHEM, INC. and ENZO LIFE SCIENCES, INC. Defendants and Counterclaim Plaintiffs.	)	04 CV 4046 (RJS)

ENZO'S RESPONSIVE *MARKMAN* BRIEF RELATED TO
U.S. PATENT NOS. 4,943,523 AND 5,082,830

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Enzo responds here to Roche's proposed constructions of the disputed claim language of the '523 and '830 patents. (D.I. 144) ("Roche Br.").[1] Roche's proposals violate numerous controlling principles of claim construction and ignore the plain and broadly-worded language of the claims, by improperly rewriting them with limitations not in the claims nor required by the specification. *Liebel-Flarsheim Co. v. Medrad, Inc*., 358 F.3d 898, 906 (Fed. Cir. 2004) ("Even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction.").

Enzo's constructions, on the other hand, fully comport with the actual language of the claims and how persons of ordinary skill in the field would have understood them.

I. PROPOSED CONSTRUCTIONS

A. The '523 Patent

Roche's unsupported assertion that "the claimed formula *would be meaningless* if it were divorced from the actual synthesis of the detectable molecule…." (Roche Br. at 6) ignores the reality that a patent can disclose multiple separate and distinct inventions (e.g., composition of matter, process, method of use, etc.) but need only claim one of them. *In re Berg*, 140 F.3d 1428, 1435-36 (Fed. Cir. 1998) (citing Manual of Patent Examining Procedure § 806 and 35 U.S.C. § 121). It also conveniently ignores that the Patent Office affirmatively "divorced" the separate and patentably distinct inventions disclosed in the '523 patent from each other during prosecution of the '440 patent. Indeed, contrary to Roche's position, the '523 patent unambiguously describes the detectable

[1] Unless otherwise noted, all exhibits referenced herein are attached to the Declaration of Jennifer R. Moore, submitted concurrently herewith. Documents already in the record are referred to by docket number. Unless otherwise indicated, all emphasis in this brief has been added. Enzo also concurrently submits the Declaration of David H. Sherman in Support of Enzo's Responsive *Markman* Brief ("Sherman Decl.").

molecules and the synthetic processes for making and methods of using them as separate and different aspects of the invention:

> In a preferred embodiment, another aspect of the invention comprises a detectable molecule of the formula (VII): $A^3—(—X—R^1—E—Det^b)_m$
>
> * * * *
>
> Other specific aspects of the invention comprise individual nucleotides, saccharides or amino acids modified with a group X-R1-E-Det as above. Still other aspects of the invention relate to synthetic methods of preparing, as well as general methods of using the aforementioned products[.]

(D.I. 143-1 ('523 patent) at 3:66-68; 4:63-68 and claims.) The PTO confirmed this by issuing a "Restriction" requirement during prosecution of the '440 patent holding, *inter alia*, that the disclosed "methods of making compounds" and "detectable and non-detectable molecules" (in ***both*** of the '440 and '523 patents) are patentably distinct inventions which could not be claimed together in the same patent but needed to be claimed in separate patents.[2] (Ex. 1 at 2-3.) In response, Enzo did not elect to pursue any method of synthesis claims in either of the '440 or '523 patents but instead proceeded with "detectable molecule" claims in both. (Ex. 3 at 4-5; Ex. 4.)

Despite acknowledging that a "detectable molecule [is] claimed in the '523 patent," Roche improperly focuses its proposed constructions on the chemical "job" of each element "in terms of *synthesis* of the resulting detectable molecule." (Declaration of Dr. Leighton ("Leighton Decl.") at ¶¶ 14, 16-17; Roche Br. at 5.) Since the claims of the '523 patent are not process claims or product-by-process claims,[3] however, Roche's approach is directly at odds with the actions of the PTO as well as

[2] Presumably this is why Roche never took the position in the parties' earlier claim construction proceedings before Judge Sprizzo that the identical language in the '440 patent compound claims would be "meaningless" if divorced from the chemical synthesis. (*See* Exs. 10-12; D.I. 143-16 and 143-17.)

[3] Enzo could have sought (but did not) '523 claims to products made by a particular process or synthesis by way of so-called "product-by-process" claims. *See Lupin Ltd. v. Abbott Labs*., 484 F.Supp.2d 448, 464-65 (E.D.Va. 2007)("product-by-process claims have been found where the claims used language such as 'prepared in accordance with,' 'by the process of,' 'product of the process,' 'resulting from the process of,' and 'being produced by the process comprising.'")

the governing claim construction authorities which prohibit reading process limitations into claims directed to products. *Vanguard Prods. Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2000) ("The method of manufacture, even when cited as advantageous, does not of itself convert product claims into claims limited to a particular process"); *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1357 (Fed. Cir. 2003) ("[W]e decline to superimpose a process limitation on the product claims at issue."). Enzo respectfully submits that the Court should reject Roche's attempt to now revisit claim constructions completed long ago to improperly import such process limitations into the compound claims of the '523 "with an aim to … exclude an accused product. . . ." *Wilson Sporting Goods Co. v. Hillerich & Bradsby Co.*, 442 F.3d 1322, 1326-27 (Fed. Cir. 2006) (improper to "prejudge the ultimate infringement analysis by construing claims with an aim to include or exclude an accused product or process[.]") (Sherman Decl. ¶¶10-21.)

1. [at least one modifiable] "reactive group" [consisting of amino, hydroxyl, 1,2-cis diOH, halide aryl, imidazoyl, carbonyl, carboxyl, thiol or a residue comprising an activated carbon]

This "reactive group" limitation is self-defined in the claim by a highly specific list of chemical groups (i.e, "amino, hydroxyl, 1,2-cis diOH, halide aryl, imidazoyl, carbonyl, carboxyl, thiol or a residue comprising an activated carbon"). Neither Roche nor any of its experts dispute—back in 2005 or now— that claim 1 lists "particular" reactive groups, or that their exact structures were "known in the art before January 1984." (Leighton Decl. ¶¶ 16, 43; Roche Br. at 6.) Thus no further construction is needed, and the list of chemical groups should control.

Roche seeks to supplant this explicitly claimed list with non-specific "functional group" language and an unstated process requirement that such group "undergoes a reaction" to bond with X "during synthesis" – a position which even its own expert admits is "***[o]utside the context*** of the '523 patent." (Leighton Decl. ¶ 41.) Indeed, the claim requires nothing of the sort, and

does not concern itself with how one of the modifiable reactive groups (or X or any of the other claimed components) becomes part of the detectable molecule of the invention, or with its alleged "purpose." Rather, it only calls for at least one of the listed modifiable reactive groups to be present in the compound as claimed. Absent an express requirement to do so in the intrinsic record, such unexpressed and unnecessary process limitations should not be read into the claim. *Vanguard*, 234 F.3d at 1372; *Cordis*, 339 F.3d at 1357. (Sherman Decl. ¶¶ 22-27.)

2. at least one "modifiable" reactive group / "modified" reactive groups

Roche's contention that the terms "modifiable" and "modified" somehow render the '523 claims invalid as indefinite should be rejected as untimely-raised as well as on the merits. Indeed, Roche's newly-minted argument was never presented in its court-ordered Invalidity Contentions (*see* D.I. 143-18 at 11). For this reason alone, it should be disregarded.[4]

On the merits, Roche contends the terms "modifiable" and "modified" are indefinite (or incapable of construction) because "it is unclear how many of the reactive groups on A^3 were modified during the synthesis and/or remain modifiable after the synthesis in the final, claimed molecule." (Roche Br. at 7.) However, even standing alone in isolation (as Roche improperly attempts to read them), the words "modifiable" and "modified" carry a plain meaning that would be readily understood by a POSA. Moreover, when read in their proper context of the rest of the claim language, and the '523 patent specification, the plain meaning and import of these terms is confirmed and fully supported. Indeed, as addressed immediately above (Section A.1), the patent identifies precisely what a "modifiable" reactive group is in the list of chemical groups (i.e., an "amino,

[4] In its Invalidity Contentions, Roche took the position that the ***entirety*** of the phrases "at least one modifiable reactive group" and "modified reactive groups" rendered the claims indefinite as opposed to only the words "modifiable" and "modified". If anything, Roche's proposed construction of the modifiable and modified "reactive group" claim terms undercuts both its original and new indefiniteness positions. *See* Section A.1. Notably, in 2005, when dealing with identical claim language in the '440 patent, neither Roche gave no indication of being unable to construe these terms nor raised an indefiniteness issue in briefing before Judge Sprizzo.

hydroxyl, 1,2-cis diOH, halide aryl, imidazoyl, carbonyl, carboxyl, thiol or a residue comprising an activated carbon"). There is nothing "unclear" at all about that list.

The answers to the "questions" and examples (A and B, p. 10) presented for the first time in Roche's opening brief (pp. 7-11) are just as straightforward. For instance, with respect to "how many of the claimed reactive groups [are] modified," a POSA would understand that a "modified" reactive group simply refers to whichever (i.e., one or more) of the listed "modifiable" reactive groups are part of an attached label as per the claimed formula. (Sherman Decl. ¶¶28-34.) Thus, "each" and every one of the reactive groups need not be "modified." (Roche Br. at 9) Nor "must" the claimed molecule "continue to have" at least one group that is not modified. (*Id*.) Per the claims, the detectable molecule can have both modifiable and modified reactive groups or only modified groups.

Furthermore, what happens during synthesis does not matter and nothing in the claim or the patent specification "requires" that "'one, several, … [or] all' of the reactive groups" become "modified during synthesis." (*Id*.) Rather, the patent simply and clearly ***allows*** for "one, several and possibly all reactive residues" to be "modified" (D.I. 143-1 at 7:7-9; Sherman Decl. ¶ 29.) As such, it would only be routine matter "to those of ordinary skill in the art to estimate . . . how many such residues have reacted, in order to determine the final stoichiometry" and thereby ascertain exactly how many "modified" groups are present in the compound. (D.I. 143-1 at 7:15-20; Sherman Decl. ¶ 31.) In this sense, Roche has miscast Enzo's claim construction position (Roche Br. at 10); it is not that "modifiable" and "modified" mean the same thing, but rather Enzo's construction is that not all "modifiable" groups need be "modified" (though they can be). This construction is plainly supported by the specification, which explains that "[i]n most instances [but not all], the number of actually modified groups will be less than the number of potentially available modifiable groups of any particular chemical species." (D.I. 143-1 at 7:23-26.) That is precisely why "m" can

be anywhere "from 1 to the total number of modified reactive groups." (*Id.* at claim 1.) That is also why, with respect to Roche's Figs. 4A and 4B, a POSA would not be confused over whether the claimed invention covers molecule A (all modifiable reactive groups modified) or molecule B (some, but not all, modifiable groups modified) – but would readily understand the claimed invention to encompass them ***both.*** (Roche Br. at 9-10.) Accordingly, the terms "modifiable" and "modified" are amenable to construction and Roche has failed to carry its heavy burden of proving them indefinite.[5]

3. "*E*" [is O, NH or an acyclic divalent sulfur atom]*

Like the disputed "reactive group" term, the patent claim provides a distinct meaning of "E" by listing out the three possibilities for it: "O, NH or an acyclic divalent sulfur atom." That definitive list should end the inquiry. Yet despite Roche's apparent agreement that "claim 1 defines E ***very specifically***, right down to the type of sulfur atom required" (Roche Br. at 12; Leighton Decl. ¶ 53), it again improperly seeks to read in an additional unstated requirement that E previously "underwent a reaction to form a bond to R^1 or Det^b."[6] (Roche Br. at 12.) Nothing in the claim requires anything of the sort or speaks to any of Roche's alleged "critical" synthetic reaction. The claim simply requires "E" to be present in the compound as claimed in the formula. Roche's unduly narrowed construction should be rejected.[7] *Liebel-Flarsheim*, 358 F.3d at 906. (Sherman Decl. ¶¶ 41-45.)

[5] Roche's reliance on statements in file histories with respect to different claims and patents are inapposite. What matters is that with the PTO having reviewed and granted the claims at issue, they are presumed to be valid and definite. And, Roche's unsupported arguments and faulty logic fall far short of the clear and convincing evidence required to overcome that presumption.

[6] It bears repeating that Roche never proposed a construction of "E" for the related '440 and '269 claim construction proceedings that required the unstated limitations it now proposes.

[7] The motive behind Roche's untenable construction is revealed in its expert's declaration where he indicates Roche's "Compound III" would meet this claim element absent adoption of Roche's proposed construction. (Leighton Decl. ¶ 55.)

4. "comprising"

Roche agrees with Enzo that "comprising" is presumptively open-ended (Roche Br. at 12), but then proposes only a semi-open construction that would allow for "additional atoms used to link the label" but nothing else. Once again, Roches bases its customized narrowing on the same faulty and unsupported premise—i.e., that Det[b] "*must* be understood in the context of the reactions by which the claimed molecule is made." (*Id.* at 13.) Roche's attempt to partially confine the established meaning of this term of art "in the context of" unspecified (and unclaimed) "reactions" by which the compounds are allegedly made, and/or certain preferred examples in the specification, is legal error and insufficient to overcome its presumptive scope, where neither the claim nor specification invite or require it. *Kara Tech. Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1345 (Fed. Cir. 2009). (Sherman Decl. ¶¶ 46-48.)

5. "biotin"*

The parties agree that in the context of the '523 patent, "biotin" must be construed to include ***some*** form of modification of naturally-occurring "biotin" as that term found in dictionaries. (*See* Sherman Decl. ¶ 49; Leighton Decl. ¶¶ 28, 61.) Roche's proposed construction "is the structure of biotin that is found in nature, ***except*** "it is missing an OH (hydroxyl) group, indicated by the red circle." (Leighton Decl. ¶ 61.) Indeed, Roche began by advocating for the naturally-occurring structure of biotin (Ex. 5), but was forced to recognize that a POSA would read this term to cover only a biotin molecule that has been "modified".[8] Thus, the question is what sort of modified biotin would a POSA understand to be covered by the claims?

Roche argues this term should be limited to modification by removal of an OH group. To answer this question, however, a POSA is presumed to look to the patent specification to ascertain

[8] Enzo's interrogatory response cited by Roche is consistent, indicating that this claim term covers a "modified biotin molecule". (D.I. 139-8 at 3.)

the breadth of the contemplated modifications. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) ("the specification necessarily informs the proper construction of the claims"). Having done so, a POSA would see, as Roche's expert, has acknowledged, that the patent broadly contemplates a variety of modifications of naturally-occurring biotin including "biotin and analogues thereof," "biotin moieties," and "biotin, or a modified biotin molecule" which "can be used as detectable molecules wherever biotin/avidin or biotin/streptavidin-based pairs have been used in the prior art." (Leighton Decl. ¶ 62; D.I. 143-1 at 3:33; 3:37; 5:3 and 8-12; 7:62; Table 1, Claim 37.) Thus, while a POSA may recognize Roche's proposed modified biotin molecule to be covered by the claim, he/she would not read the '523 patent as restricting "biotin" to only that one modification but would read it more broadly, consistent with the patent and Enzo's proposed construction. (Sherman Decl. ¶¶ 49-51.)

6. "chelator"

The parties agree that the principal dispute over this term is whether, in the context of the '523 patent, a chelator becomes part of a chelate when it complexes with a metal ion. On this, the patent claims and specification expressly support Enzo's position that it does. (*See*, *e.g.*, D.I. 143-1 at 7:61-8:18; 8:40-9:9; Sherman Decl. ¶¶ 52-58.) Roche's attempt to use extrinsic information "to vary or contradict the claim language" and "other parts of the specification" should be rejected because "the intrinsic evidence alone will resolve any ambiguity" in this disputed claim term. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583-84 (Fed. Cir. 1996). Roche's position is also directly contradicted by the testimony of its own scientists (and Rule 30(b)(6) witnesses):

> A chelator is a ligand with two binding sites to the metal atom. So if you talk about a chelate -- and I think this is a term --"chelate" is an abbreviation. It's not a term which has an official meaning. The chelate from my experience is used for the abbreviation of "metal chelate", and chelator, as I said, is a ligand with this behaviour. ***So a chelator is part of a metal chelate***, if we stick to the terminology. (D.I. 143-11 (9/19/13 Ofenloch-Haehnle Depo) at 148-18-149:2; *see also* D.I. 143-12 (9/19/13 Huber Depo) at 86:3-9.)

7. "compound capable of yielding a metal chelator"*

Roche again asks this Court to read an unstated method limitation into the clear language of this "compound" claim term. Nothing in the claim or the patent, however, requires that the claimed compound only be capable of yielding a metal chelator during "the detection process." Recognizing this, Roche does not even attempt to ground its construction in the '523 patent. Instead, the sole support cited by Roche is a portion of a clarifying statement made in the prosecution history of a different patent (the '440), with respect to different claims.[9] This is not the clear, deliberate and unmistakable disavowal of claim scope with respect to the '523 claims at issue that is required by law. *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1325-26 (Fed. Cir. 2003) ("the alleged disavowing statements [must] be both so clear as to show reasonable clarity and deliberateness, and so unmistakable as to be unambiguous evidence of disclaimer."); *see also NMT Med., Inc. v. Cardia, Inc.*, 239 F. App'x 593, 600 (Fed. Cir. 2007) (statements made to clarify indefiniteness rejections did not unambiguously surrender claim scope). (Sherman Decl. ¶¶ 52-58.)

8. "a residue comprising an activated carbon"

Raised for the first time in its opening claim construction brief,[10] Roche's untimely position also suffers from the same fatal flaw as Roche's other constructions of adding unrecited process limitations into a claim to a compound. *Vanguard Prods.*, 234 F.3d at 1372; *Cordis Corp.*, 339 F.3d at 1357. (Sherman Decl. ¶¶ 35-40.)

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[9] Notably, Roche failed to raise this disclaimer argument during the '440 patent claim construction proceedings before Judge Sprizzo.

[10] This construction is different than what Roche originally proposed in the parties' JCCS. There, Roche said this disputed term should mean "a monomer *that is present in a polymer*, which monomer contains an aromatic carbon atom that is capable of covalently reacting with an electrophilic compound." (D.I. 143-3 at 9 (deleted language italicized).) Roche's new position should be rejected by the Court as untimely. (*See* D.I. 99 and 128.)

Indeed, Roche's only argument for reading the compound language of a "residue comprising an activated carbon" to mean "a monomer which contains an aromatic carbon atom that is capable of covalently reacting with an electrophilic compound" is that certain embodiments in the patent specification allegedly describe these types of activated carbon reactive groups (JCCS; Leighton ¶ 76; Roche Br. at 17.) But since Roche can point to nothing in the specification (let alone the claim language) which actually requires such a narrow definition, this attempt to read it in from examples violates one of the most basic principles of claim construction law. *Liebel-Flarsheim*, 358 F.3d at 906.

9. "said complex"

In Roche's own words -- its proposed reading of claim 15 as requiring a "step of 'separating' a complex from itself" is nonsensical. (Roche Br. at 18.) Enzo agrees, and so would a POSA who would never read the claim in such a non-sensical way. (Sherman Decl. ¶¶ 59-62.) Rather, a POSA would understand the claim term "said complex" of element (b) to refer back to the previously recited "composition" of element (a). Indeed, in patent parlance, the word "said" is meant to indicate to the reader/POSA that the term it modifies has been previously recited. Thus, since "composition" was previously recited in (a), a POSA would understand the term "said" in element (b) to be referring to it. Moreover, this reading is confirmed and supported by the very next limitation of element (c) which refers to a "detectable" complex because the "composition" of element (a) is explicitly claimed to comprise the "detectable" molecule (of claim 1). Roche fails to give any reason why a POSA would choose its admittedly nonsensical reading over Enzo's sensible construction (and/or why all of this would not be recognized as an obvious error and/or subject to reasonable debate).[11]

[11] Roche's citation to claim 2 actually supports Enzo's position. As the claim language and the specification make clear, the composition comprises the detectable molecule, and the A3 portion of the detectable molecule is the only site to which the analyte binds. (D.I. 143-1, claim 2 and 15.) Therefore, there is no principled difference between separating the analyte and the *composition* versus

B. The '830 Patent Disputed Claim Terms

Roche takes a very similar overly-restrictive approach in construing the '830 patent claims. Although Roche does not seek to import process limitations into the broad and previously-construed language of the '830 claims, it does repeatedly try to read in various unstated functional or structural restrictions that are neither invited nor required by the claims. (Sherman Decl. ¶ 65.)

1. "oligo- or polynucleotide"

a. "Probe". Roche's first mistake in its proposed construction is to try to limit the claimed "oligo- or polynucleotide" to a "nucleic acid probe." Roche gives only lip service to construing this language in the "context of the patent claims" (Roche Br. at 20), because the language of the claims plainly does not invite or require such a limitation. Absent an express requirement to do so, it should not be imported. *See Kara Tech.*, 582 F.3d at 1345. The legal prohibition against Roche's proposal is even stronger in this instance where more than a dozen other claims (claims 18-32) of the '523 patent affirmatively and intentionally include the limitation of a "probe" but the claims at-issue do not. *AllVoice Computing PLC v. Nuance Comm'ns, Inc.*, 504 F.3d 1236, 1247 (Fed. Cir. 2007) (limitation not read in where "would render additional, or different, language in another independent claim superfluous.")

Moreover, as Roche admits, a "probe" is defined by its function: "A nucleic acid probe is a sequence of nucleotides that is designed to hybridize to a target nucleic acid sequence to detect the target sequence." (Cantor Decl. ¶ 46.) Where a function is not recited in the claim itself by the patentee, courts do not import it as a limitation. *Ecolab, Inc. v. Envirochem, Inc.*, 264 F.3d 1358, 1367 (Fed. Cir. 2001); *Toro Co. v. White Consolidated Indus., Inc.*, 266 F.3d 1367, 1371 (Fed. Cir. 2001) ("An invention claimed in purely structural terms generally resists functional limitation.")

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separating the analyte and the *detectable molecule*. Accordingly, although Enzo believes it to be unnecessary the Court's construction could merely repeat what is already stated in the claim, i.e., that "said complex" refers to the claimed "composition which comprises the detectable molecule."

Roche effectively ignores these controlling legal authorities and plain language of the '830 patent claims, basing its construction on the Title of the patent and selective quotes from the specification. But, the title of a patent is "near irrelevan[t]" to claim construction and "is not to demarcate the precise boundaries of the claimed invention but rather to provide a useful reference tool for future classification purposes". *See Pitney Bowes, Inc. v. Hewlett-Packard Co*., 182 F.3d 1298, 1311-12 (Fed. Cir. 1999). Thus, it cannot trump the plain language of the claims addressed above and/or the descriptions of the patent specification. As for the specification, Roche quotes only certain snippets, omitting the opening sentence of the '830 patent which broadly indicates that the "invention relates to signal generating systems for specific binding assays" (D.I. 143-2 at 1:5-7.) The patent also goes on to express broad applicability to "any compound or composite capable of recognizing a particular spatial and polar organization of a molecule" with a "probe" identified as one example ("such as a nucleic acid hybridization assay probe"). (*Id*. at 3:9-19.)[12] This falls far short of the express restriction that the law requires to limit the claims. *Abbott Labs. v. Baxter Pharmaceutical Prods., Inc.,* 334 F.3d 1274, 1279-80 (Fed. Cir. 2003). (Sherman Decl. ¶¶ 66-73.)

b. "Naturally-Occurring" Nucleotides. Roche's other argument that the claim is restricted to only "non-naturally occurring nucleotides because there is "nothing in the intrinsic evidence to suggest that the inventors intended to claim modified nucleotides generally" is equally flawed. Once again, it ignores the most probative evidence for purposes of claim construction -- the claims themselves. Indeed, when a 'non-radioactive moiety" is attached to a nucleotide, that nucleotide

[12] Enzo did not limit the invention to probe-use during prosecution in either the U.S. or abroad. First, the European prosecution is entitled to very little weight because of the different patents and laws involved. *See, e.g.*, *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1290 (Fed. Cir. 2006). More importantly, Enzo never distinguished the claimed invention as patentable over the prior art based on its use as a probe because the prior art was directed to probes. (D.I. 140-7 at 15 ("McCormick discloses a probe ...."; "Lear et al disclose biotin-labeled DNA probes ...."; D.I. 140-8 at 3 ([reference] is directed to a hybridization assay method ... using two polynucleotide probes.") Thus, there could be no clear and unmistakable disclaimer of non-probe-uses. *Omega Eng'g*, 334 F.3d at 1325-26.

necessarily becomes "modified" from its so-called natural form. (Sherman Decl. ¶ 75.) Thus, counter to Roche's argument, because the oligo- and polynucleotides of the claims have end nucleotides with a substituted/attached moiety the plain language of the claims does not exclude, but necessarily and explicitly cover and include, "modified" and/or non-naturally occurring nucleotides. Likewise, nothing in the patent specification mentions or parses out "naturally-occurring" versus "non-naturally occurring" nucleotides. Accordingly, Roche cannot point to any "words of manifest restriction or exclusion" that would so limit the claims. *Liebel-Flarsheim*, 358 F.3d at 906.[13] (Sherman Decl. ¶¶ 74-79.)

2. "having"*

Neither Roche nor its expert have cited *any* evidence from the patent that excludes additional elements from the claims.[14] The claims merely require an oligo- or polynucleotide that has non-radioactive moieties attached at the 5' and 3' ends. Additional elements attached to the non-radioactive moieties themselves are within the scope of the claims. (Sherman Decl. ¶¶ 80-81.)

3. "at least one non-radioactive moiety … attached to each of the 5' and 3' end [terminal] nucleotides"

Here again Roche's formulated its construction on its non-infringement theory, and its references to "products like Roche's" (Roche Br. at 23) exceed the proper role of providing

[13] Judge Sprizzo's construction of the unrelated '955 patent is wholly irrelevant to the construction of the '830 patent. *See Goldenberg v. Cytogen, Inc.*, 373 F.3d 1158, 1168 (Fed. Cir. 2004)("Absent a formal relationship or incorporation during prosecution, the new-matter content of the '744 patent is not available to construe the claims of the '559 patent, and the district court erred in relying on them."); *Abbott Labs. v. Dey L.P.*, 287 F.3d 1097, 1104-05 (Fed. Cir. 2002).

[14] Roche mis-cites *Pieczenik v. Dyax Corp.*, 76 F. App'x 293, 296 (Fed. Cir. 2003) for the proposition that in ***all cases***, "substituting 'comprising' for 'having' would read the specificity … out of the claim." (Roche Br. at 22.) In *Pieczenick*, the patentee "became a lexicographer and particularly defined 'oligonucleotide.'" *Id.* at 298. Moreover, the claimed oligonucleotide had a coding region of a specific length—i.e., "***having*** a length from about 4 to about 12 nucleotide triplets." *Id.* at 296. Interpreting "having" to mean "comprising" would have read "specificity—***in particular, the upper bound of 'about 12'***—out of the claim." *Id.* at 296. In contrast, the claim language of the '830 patent contains only a lower bound—"at least one" non-radioactive moiety attached at "each" end.

"meaningful context" to claim construction. *Wilson Sporting Goods*, 442 F.3d at 1326-27. "Enhance the signal generating output" is claim term, and since the parties adopted the Federal Circuit's construction of the term "non-radioactive moiety," it would be impermissible to allow Roche to import unstated limitations into the claims, particularly when there is no specific claim language to interpret. *Purdue Pharma L.P. v. Endo Pharma Inc.*, 438 F.3d 1123, 1136-37 (Fed. Cir. 2006).

Roche gives no reasonable explanation why the Court should import the unstated functional limitation of "to enhance the signal generating output" into the claims. First and foremost, the non-functional structural language of the claims do not require it. *Ecolab*, 264 F.3d at 1367. Likewise, the Federal Circuit's prior claim construction of the '830 claims does not even mention it, let alone require it. *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1340 (Fed. Cir. 2010). Finally, as recognized by Roche in other sections of its brief (pp. 19 and 20), the patent specification describes multiple other ***possible*** benefits of the invention including "greater stability" and "reduced disruption of hybridization" and Roche provides no justification for limiting the claims to just one of them.[15] (D.I. 143-2 at 1:5-6; 11:68-12:2; D.I. 140-7 at 20; Sherman Decl. ¶¶ 82-86.)

4. "5' and 3' end nucleotides"

As noted in our opening brief, for purposes of these claim construction proceedings, Enzo does not dispute Roche's construction—even though, per the patent, "at the 3' and/or 5' ends" refers to nucleotides near to, but not themselves the termini (*see, e.g.*, D.I. 143-2 at 11:65-12:3 - oligomer 8). (Sherman Decl. ¶ 87.)

[15] Again, Roche's reliance on a European prosecution history is entitled to little to no weight (see n. 14 above), as is Roche's cite to extrinsic testimony of an inventor, particularly this particular inventor who was involved in the synthesis of the labeled oligonucleotides but testified to not having expertise or involvement in their functionality. *See Howmedica Osteonics Corp. v. Wright Med. Tech., Inc.*, 540 F.3d 1337, 1346-47 (Fed. Cir. 2008).

5. [at least one non-radioactive moiety directly or indirectly attached to each of the] "5' and 3' terminal nucleotides external to a target hybridization region"

Roche argues plain language of the claim, but then ignores that language, presenting only parts of the claim as opposed to the full and complete language [in brackets above] which, when read in proper context, makes clear that it is the attached non-radioactive moieties, and not the nucleotides, that are "external" to the hybridization region. Enzo's reading is the only one which makes sense, because the terminal nucleotides would be understood by a POSA to hybridize and thereby be part of a hybridization region. This is confirmed by the preferred examples in the specification, the vast majority of which would be excluded from the claim by Roche's reading because the end nucleotides (no matter how defined) actually hybridize. *Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1290 (Fed. Cir. 2010) ("A claim construction that excludes the preferred embodiment 'is rarely, if ever, correct and would require highly persuasive evidentiary support.'"). (*See* D.I. 143-2 at Table 1; Sherman Decl. ¶¶ 88-92.)

II. CONCLUSION

For the foregoing reasons, Enzo requests that the Court adopt its proposed constructions of the disputed claim terms, and hold as a matter of law that the asserted claims are definite.

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